REMARKS

This Amendment and Remarks are filed in response to the Final Office Action dated May 19, 2003 wherein all pending claims stand rejected.

Status of the Amended Claims

Claim 19 is amended to be directed against the antibody produced against a recombinant *Cryptosporidium* antigen depicted by SEQ ID NOs: 4-6 which antibody binds to both the recombinant or native antigen of the same amino acid sequences. Support is found in the Specification, page 27, line 8-15.

Claim 20 is limited to the antibody binding the fragment of the amino acid sequence SEQ ID NO: 5.

Claim 21 is limited to the antibody binding the fragment of the amino acid sequence SEQ ID NO: 6.

Claim 22 is unchanged.

Claim 23 is amended to better define the antigen and the complex.

Claim 24 is amended to correct the dependency.

Claim 25 is amended to correct the dependency.

Claim 40 is amended to become independent claim directed to the antibody suitable for treatment fo *Cryptosporidium* infections wherein said antibody is produced against the recombinant cryptopain antigen depicted by SEQ ID NOs: 4-6 which antibody binds to both the recombinant or native antigen of the same amino acid

sequences. Support is found in the Specification, page 27, line 8-15, support for therapeutic activity of the antibody is found at page 8, line 6-12, page 31, lines 25-33 and page 32, lines 1 and 2.

Claim 41 is limited to the antibody binding the fragment of the amino acid sequence SEQ ID NO: 4.

Claim 42 is limited to the antibody binding the fragment of the amino acid sequence SEQ ID NO: 5.

Claim 43 is limited to the antibody binding the fragment of the amino acid sequence SEQ ID NO: 6.

Claim 44 is amended to become independent claim directed to a polyclonal or monoclonal antibody suitable for detection of *Cryptosporidium* infections wherein said antibody is produced against the recombinant cryptopain antigen depicted by SEQ ID NOs: 4-6 which antibody binds to both the recombinant or native antigen of the same amino acid sequences. Support is found in the Specification, page 27, line 8-15.

Claim 45 is amended to better define the antibody/antigen complex.

Claim 46 is amended to better define the antibody/antigen complex.

Claim 47 is amended to better define the antibody/antigen complex.

Claim 48 is amended to better define the antibody/antigen complex.

Claim 49 is amended to better define the antibody/antigen complex.

Rejections Under 35 USC 102(a)

Claims 19-24 and 40-49 are rejected under 35 USC 102(a) as being anticipated by Nesterenko et al.

Examiner maintains his prior rejections and argues that Nesterenko discloses antibodies that bind to a surface antigen proteinase of 24kD associated with sporozites of *Cryptosporidium parvum* from fecal specimens. This surface antigen protease was inhibited by inhibitors of both metalloproteinases and thiol proteinases, but not serine or aspartyl proteinase inhibitors. The sensitivity of the membrane-associated cysteine protease to inhibitors is similar to that of the metallo-activated cysteine proteinases calpain I and II. Therefore, the evidence seems to suggest that Nesterenko's cysteine protease is the same antigen that comprises SEQ ID Nos: 4-6 of the instant application, and antibodies to this antigen inherently meet the limitations of the instant claims given the evidence at hand and absent evidence to the contrary. Applicant's arguments filed February 24, 2003 have been fully considered by they are not persuasive.

Applicants disagree and will deal with Examiner rejections and response to prior Applicants arguments in the same sequence as raised by the Examiner.

First, Applicants amended claims 19-25 and 40-49 to be directed to the antibody against cryptopain antigen depicted solely by the amino acid sequences SEQ ID NO 4-6. This antigen is specifically identified as 401 amino acid protein of 45 kD SEQ ID NO: 4 or as its fragment SEQ ID NOs: 5 or 6, which are specifically identified as having a MW 25 kD. Applicants respectfully submit that the claimed antibody is not the same antibody as that of antibody disclosed by Nesterenko.

The Nesterenko protease is described as 24 kD, compared to the cryptopain protease having a molecular weight of 45 kD. Nesterenko does not identify it as a fragment but as a whole protease having that size. Applicants, on the other hand identify the whole cryptopain protease as having 45 kD (page 10, lines 28-33, page 11, lines 1-5 with its mature portion of 226 amino acid protein of MW 25 kD. The DNA sequence of 1203 nucleotides encodes the 45 kDa protein SEQ ID NO: 4, the cathepsin-like cysteine proteinase cryptopain page 12, lines 24-27).

Examiner dismisses the difference in the MW between the Nesterenko protease and currently claimed cryptopain as irrelevant and due to a laboratory experimental error, but it is not so. One cannot mix apples and oranges at will. If the compared subject is the whole protein, and the cryptopain protease is the whole protein, then the respective molecular weights and the behavior and/or presence of such protein and their metallo-dependency or

independency are also important in distinguishing the invention from the reference. In this case, the applicants whole protein has MW 45 kD and its fragments' MW is 25 kD. The current cryptopain is metallo-independent either surface or internally localized antigen. Nesterenko's protease has MW 24 kD, is a surface antigen and metallo-dependent.

As to the molecular weight, one dalton is defined as a unit mass equal to 1.65×10^{-24} gm. One kilodalton is 1000 times that amount. The difference in molecular weight between $24 \times 1.65 \times 10^{-24} \times 1000$ of Nesterenko protease (39,600 mass units) and 45 or 25 $\times 10^{-24} \times 1000$ of the cryptopain (74,250 or 41,250 mass units) is either 34,650 mass units for 45 kD protein or 2,350 mass units for 25 kD protein.

If the compared subject is the antibody raised against the specific antigen, such as the one disclosed by applicants having a very precise and specific amino acid sequence and molecular weight of 45 kD, 34,650 mass units larger, or 25 kD, 2,350 mass units larger then the protein of the Nesterenko reference, then the difference in the molecular weight cannot be valiantly dismissed as unimportant due to the laboratory error. Examiner does not present any evidence showing that the 45, 25 and 24 kD proteins are the same and/or that there was an experimental error in Applicants determination of amino acid or DNA sequences of relevant proteins SEQ ID NOs: 4-6.

Applicants maintain that 24 and 25 and 45 kD proteins are not the same and that cryptopain of the invention is not protease of Nesterenko and therefore the antibody raised against cryptopain are not the same as those raised against protease of Nesterenko.

Applicants now amended claims only to the antibodies raised against the antigen having those specific amino acid sequences and different molecular weight from the protease of Nesterenko.

Moreover, the claimed antibodies are raised against the recombinant molecules thus ever further distinguishing them from the proteases of Nesterenko whose antibodies were eluted directly from nitrocellulose blots (Abstract) or produced naturally (page 80, last full paragraph and page 81, the first paragraph).

Examiner further responded to prior Applicant's arguments filed February 24, 2003 having not found them persuasive because Applicant argues that Nesterenko's antibodies were not associated with oocyst walls, rhoptries or microneme which are internal structures and the surface localization of Nesterenko's antibodies is consistent with the Examiner's observation that Nesterenko's antibodies bound to a surface antigen protease.

Although in view of the new amendments and arguments showing that the current cryptopain is different than the protease of Nesterenko, this argument is moot, Applicants want to point out that, unfortunately Examiner's observations cannot be used to support otherwise unrefutable evidence stated by both the

Nesterenko and by the Applicants. The fact remains that the Applicants cryptopain is found either on the surface or internally positioned and gets to the surface during the invasion as shown by the use and testing of specific inhibitors as shown in Figure 10, as discussed in greater detail in the prior response to the Office Action. Applicants do not say that their protease is the surface or is not the surface, only that their results show that is can be surface or it can be internal and released during the invasion. That is not the same as Nesterenko who clearly states in the Abstract: "An indirect immunofluorescence assay using these monospecific antibodies revealed that the protease occurred on the surface of sporozoites, but was not associated with oocyst walls, rhoptries or micronemes." (Abstract)

Examiner finds the simpler explanation for the experimental results seen in Figure 10 that, to make the reasonable conclusion based on the evidence that cryptopain is a surface antigen, absent evidence to the contrary such as data explicitly showing its internal location or translocation to the surface.

Applicants again disagree. Based on above showing that the cryptopain is different protease from that of Nesterenko, the above conclusion is moot as Applicants do not claim either the surface or internally located antigen but a specific antibody raised against antigens with known amino acid sequence and molecular weight.

Finally, Examiner rejects Applicant's prior argument that

cryptopain is a cathepsin-like cysteine proteinase and is distinguished from the proteinase of Nesterenko which is inhibited by inhibitors of metalloproteinases and thiol proteinases.

Applicants again disagree. The fact that the cryptopain is not metalloproteinase dependent is just another distinguishing feature in showing that the protease of Nesterenko and the current cryptopain. Applicants do not claim this property and other then showing that the two proteases have different properties vis-a-vis metalloproteinase inhibitors bears not on the current claims.

Applicants respectfully submit that the protease of Nesterenko is not the same and is not anticipated by Nesterenko. All evidence points to the contrary. Section 102 (a requires that the invention is known or used or patented or described, in other words, that the two are the same. This is clearly not the case here.

Examiner is respectfully requested to withdraw the rejection under 35 USC 102 (a) and pass the claims to issue.

Rejections Under 35 USC 103(a)

Claims 19-22 and 25 are rejected under 35 USC 103(a) as being unpatentable over Nesterenko in view of Ramakrishnan et al. (US 5,317,510).

Examiner argues that the teachings of Nesterenko are set forth above. Nesterenko does not teach monoclonal antibodies. Ramakrishnan does teach the advantage of monoclonal antibodies which can be produced from immortalized cell lines which would then

allow unlimited production of antibodies. It would have been obvious to one of ordinary skill in the art at the time of the invention to make monoclonal antibodies to any pathogen in order that the supply of said antibodies would be steady and constant from an immortalized cell line.

Applicant's arguments filed February 24, 2003 have been fully considered but they are not persuasive because Applicant argues the antibodies of Nesterenko do not meet the claim limitations for the reasons argued in the 102(a) rejection set forth above. The Examiner believes he has successfully responded to these arguments above and so the rejection is maintained.

Applicants disagree.

Applicants have shown that the protease of Nesterenko is not the same as cryptopain of the invention. Cryptopain has not the same molecular weight, may be localized differently and is not metalloproteinase dependent. Therefore, any combination of the Nesterenko reference with the teaching of Ramakrishnan would derive, at most, a monoclonal antibodies to the Nesterenko 24 kD protease but it will not result in the monoclonal antibodies of the invention raised against the whole cryptopain or the fragment thereof.

Applicants respectfully request that in view of the above presented arguments Examiner reconsiders his rejection under 35 U.S.C. 102 and 103 and allows the pending claims to issue.

SUMMARY

In summary, Applicants substantially amended claim 19-25 and 40-49 and submit compelling arguments overcoming the rejections under 35 U.S.C. 102 and 103. With these rejection being overcome, Applicants believe that all claims are in conditions for immediate allowance. Notice of Allowance is respectfully solicited.

Should Examiner require further amendments, Examiner is requested to call the undersigned at 650-324-1677.

Respectfully submitted,

Date: August 19, 2003

Hana Verny (Reg. No. 30,518)
Attorney of Record

PETERS, VERNY, JONES & SCHMITT, LLP
385 Sherman Avenue, Suite 6
Palo Alto, CA 94306
TEL (650) 324-1677 / FAX (650) 324-1678
Atty Dkt: 480.75-2 (HV)